Container Closure System Components Composition and Selection PORI L & E Recommendations

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Introduction

Critical First Step

Careful component selection

Attention to formulation information

Allows the Pharma Development Team to:

- Obtain early information on types of potential extractables and leachables
- Develop a base of knowledge about the components which will help define selection of extraction technique(s)/method(s)
- Begin risk assessment on potential extractables/leachables
- Compare results of extraction studies with the component formulation as a check on the extraction technique(s)/method(s)

Second Critical Step

Pharmaceutical Development Team must:

- Determine the "critical components" of their product

Critical Components for OINDP

- Those that contact the patient (i.e., the mouth piece)
- Those that contact the drug formulation directly
- Those that effect the mechanics of the performance of the device
- Any necessary secondary protection packaging

Recommendations for Container Closure System Components

- The pharmaceutical development team should obtain all available information on the composition and manufacturing/fabrication processes for each component type to the extent possible, and determine which components are "critical."
- Component formulation should inform component selection.
- Risk Assessment should be performed during the selection of components and materials.
- Extractables testing, including Controlled Extraction Studies and the development and validation of Routine Extractables Testing methods, should be accomplished for all critical OINDP components.

Component Information

The Pharma Development Team should obtain all available information:

- Composition
- Manufacturing/fabrication processes for each component

Examples of This Type of Information

- The base elastomeric/polymeric material (e.g., high density polyethylene, butyl rubber, stainless steel)
- The additive composition of the component
 - Reaction/degradation chemistry
- Polymerization process plus associated polymerization/curing agents
- Fabrication process, including additives designed to assist in fabrication
- Cleaning/washing processes for finished components
- Storage/shipping environment for components and drug product

Ancillary Components

Ancillary components required by the OINDP label and which are deemed critical:

- Nebulizers
- Spacers

Example of Critical Components for a MDI

- Canister
- Elastomeric seals
- Plastic valve components
- Metal valve components
- Mouth piece

Considerations in Component Selection

- Materials, when possible, should comply with accepted standards for food contact and/or generally recognized as safe (GRAS) materials
- Materials should meet the indirect food additive regulations in Title 21 of the Code of Federal Regulations (CFR), when possible

Considerations in Component Selection

- Components containing sources of known potent carcinogens or mutagens should be avoided/minimzed, e.g.:
 - Polynuclear Aromatic Hydrocarbons (PNAs)
 - N-nitrosamines
 - Mercaptobenzothiozole (MBT)

Risk Assessment Should be Performed During the Selection of Components/Materials

- Sponsor should conduct risk assessment on the component based on supplier provided information
- Sponsor toxicologist should estimate worst-case Total Daily Intake (TDI) for ingredients
- Toxicologist can provide an estimate of risk were the components to appear in a leachables profile

Extractable Testing for Critical OINDP Components

- Extractables testing should be accomplished for critical OINDP components
 - Controlled extraction studies
 - Development and validation of routine quality control methods
 - Appropriate characterization and control of extractables profile in new patient-contact critical components should be completed

Examples Illustrating Recommendations

Knowledge derived from component composition and risk assessment

Overview of Test Articles

Working group started with test articles of known composition:

- Polypropylene
- Sulfur-cured elastomer
- Peroxide-cured elastomer

Example Composition of Sulfurcured Elastomer Test Article

Ingredient	Percent (W/W)
Calcined clay	8.96
Blane fix (barium sulfate)	25.80
Сгере	38.22
Brown sub MB	16.84
Carbon black MB	2.11
ZnO	4.04
2,2 Methylene-bis (6-tert-butyl-4-ethyl phenol)	0.56
Coumarone-indene resin	1.12
Paraffin	1.12
Tetramethyl thiuram monosulfide	0.11
Zinc 2 – mercaptobenzothiazole	0.29
Sulfur	0.84

Ingredients in Polypropylene Test Article

Chemical Name	Percent (W/W)
Tetrakis (methylene (3,5-di-t-butyl-4- hydroxy hydrocinnamate)) methane	0.08
Bis (2,4-di-t-butyl (phenyl) pentaerythritol diphosphite	0.05
Calcium stearate	0.03 – 0.4
Vegetable oil derived 90% alpha monoglycerides	0.3
3,4-dimethyldibenzylilene sorbitol	0.2

Considerations in Testing Sulfur-cured Elastomers

- Presence of carbon black polynuclear aromatics (PNAs)
- Tetramethyl thiuram monosulfide and other curing agents Nnitrosamines
- 2-mercaptobenzothiazole special case compound needing special analytical investigation
- Paraffin and coumarone-indene resin natural products likely to produce complex extractables/ leachables

Considerations in Testing Polypropylene

- High density polypropylene high levels of soluble oligomers
- Chemical properties of additives such as Irganox 1010 HPLC methods are indicated
- Complex chemical additives (e.g., Ultranox 626) desirable to obtain additives to facilitate identification
- No reason to suspect special case compounds so special analytical studies to characterize these types of entities are not needed

Summary

 No matter how detailed supplier information is, this does not preclude the need for comprehensive controlled extraction and leachable studies and appropriate risk assessment for safety